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Post-H1N1 Flu Vaccination Narcolepsy in Switzerland: A Retrospective Survey in the 30 Sleep-Certified Swiss Centers

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Key Words

Post-H1N1 narcolepsy · Narcolepsy · Vaccination · Certified sleep centers · Hypocretin

Abstract

Narcolepsy-cataplexy is a sleep-wake disorder and suggested to be immune-mediated, involving genetic and environmental factors. The autoimmune process eventually leads to a loss of hypocretin neurons in the lateral hypothalamus. Epidemiological studies in several countries proved an increased incidence of narcolepsy after H1N1 flu vaccination and infection. This survey in 30 sleep centers in Switzerland led to the identification of 9 H1N1-vaccinated children and adults as newly diagnosed narcolepsy. Clinical features included the abrupt and severe onset of sleepiness, cataplexy and sleep fragmentation.

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Introduction

Narcolepsy-cataplexy (NC or narcolepsy type 1) is a chronic neurological sleep-wake disorder with a prevalence of 25–50 per 100,000 in western countries [1]. The

'narcoleptic symptom pentad' includes excessive daytime sleepiness (EDS), cataplexy, sleep paralysis, hypnagogic hallucinations and sleep fragmentation. NC is suggested to be an immune-mediated disorder affecting genetically predisposed individuals coupled with exposure to environmental factors. The genetic background is strongly associated with the HLA-DQB1*06:02 genotype [2]. Among environmental factors, bacterial (*streptococcus pyogenes*) or viral (influenza A H1N1) infections and H1N1 vaccination have been correlated with the onset of NC [3–5]. Ultimately, the suggested autoimmune process degrades hypocretin-producing neurons in the lateral hypothalamus as the main cause of the NC symptoms [6].

Since 2010, several epidemiological observations and studies have pointed to an increased occurrence and risk (3–15 fold) of narcolepsy following H1N1 flu vaccination in autumn 2009 [4, 5, 7–10], as well as after H1N1 disease [11]. The provoking effect of H1N1 vaccination was primarily and mainly observed in children, adolescents and young adults [4, 7–10].

Different causes for the specific role of Pandemrix[®] being the pivotal trigger for post H1N1 NC are discussed (e.g. AS03 adjuvant). Recently, a higher amount of polymeric H1N1 virus nucleoprotein probably due to differ-

Table 1. Clinical, MSLT, PSG and laboratory features of post-H1N1 flu vaccination NC

	n	Post H1N1 NC patients	
		mean or %	SD or range
<i>Clinical data</i>			
Boys/men:girls/women, n	8	5:3	
Age at diagnosis, years	8	20.4	9–39
Time between vaccination and first symptoms, weeks	8	5.25	2–16
Weight gain*	8	50	
<i>NC symptoms</i>			
EDS at onset	8	100	
EDS after 1 year	8	100	
Cataplexy at onset	8	100	
Cataplexy frequency at onset, n/week	8	6.8	5.7
Cataplexy after 1 year	8	75	
Cataplexy frequency after 1 year, n/week	8	0.75	2.5
Sleep paralysis at onset	7	85.7	
Sleep paralyis after 1 year	7	28.5	
Hypnagogic hallucinations at onset	8	75	
Hypnagogic hallucinations after 1 year	8	37.5	
Disturbed nocturnal sleep at onset	8	75	
Disturbed nocturnal sleep after 1 year	8	75	
<i>MLST data</i>			
Mean sleep latency, min	8	2.00	1.56
SOREMPs (% of naps)	8	80.6	
<i>Polysomnography data</i>			
TST, min	7	413	47
Sleep efficiency	7	84	8
<i>Laboratory data</i>			
HLA DQB1 0602 positive	8	100	
CSF hypocretin < reference values	6	100	

SOREMPs = Sleep-onset REM periods; TST = total sleep time. 'Onset' is defined as within the first 6 weeks after disease onset (first symptoms).

* Weight gain is defined as an increase in weight >5 kg within 3 months after disease onset.

ent purification process was detected in Pandemrix® compared to Arepanrix® [12].

In Switzerland, 2 case reports were published in detail [13] and overall 5 cases have been reported to the Swiss authorities until 2011 [14]. H1N1 vaccination coverage in Switzerland was approximately 17%. Pandemrix® was

used in approximately 60% of all H1N1 vaccines. It was licensed for the use in adults (18–60 years) only [15]. For children and adolescents, Focetria® and Celtura® have been licensed and used [15].

There are no statistical data available on the incidence or prevalence of sporadic NC in Switzerland. The calculated number of new cases of narcolepsy in Switzerland assuming an incidence in the literature of 0.5/100,000 would be of 40 per year.

We aimed at assessing the frequency and characteristics of post-H1N1 flu vaccination narcolepsy in Switzerland.

Methods

Since patients suspected for narcolepsy are usually referred to a specialized sleep center for final diagnosis by use of MSLT, HLA typing and hypocretin analysis [16], we based our survey on the Swiss sleep centers, accredited by the Swiss Society of Sleep Research, Sleep medicine and Chronobiology (www.swiss-sleep.ch). We contacted all sleep centers for 'probable cases' of NC in context of H1N1 vaccination since 2009. In case of a positive response, centers were asked for detailed data on their cases. Data were collected and analyzed using available medical documentation of the cases. Assessment included demographic, clinical, MSLT, polysomnography (PSG) and laboratory data. Data were analyzed after anonymization.

Results

Survey

Our survey had a high response rate; 29 out of 30 (97%) sleep centers answered. Six centers reported possible H1N1-related cases of NC: Bern University Hospital, Department of Neurology (3), University Hospital Zurich, Department of Neurology (1), University Children's Hospital Zurich, Pediatric Sleep Disorders Center (1), University Hospitals of Geneva, Sleep Laboratory (1), CENAS Sleep Center, Geneva (1), University Hospital Lausanne, Sleep Center (2). For eight out of these nine patients additional details could be obtained.

Patients

In all eight patients, EDS occurred as the first symptom, followed by cataplexy and other NC symptoms a few days or weeks later (table 1).

Polysomnography

In seven out of eight patients, PSG was performed for diagnosis. In all patients, 'sleep fragmentation,' defined by poor sleep efficiency, was reported.

Family History

One patient reported a first-grade relative suffering from narcolepsy and 1 patient reported neurodermatitis. Besides this, no family history or co-occurrence of any other sleep or autoimmune disorders was reported.

Vaccines

In seven out of eight patients, Pandemrix® has been used. In 1 patient, Focetria® has been used.

Diagnostic Latency and Date of Diagnosis

Mean diagnostic latency was 13.4 months; six out of eight patients were diagnosed in 2010, 2 patients in 2013.

Discussion

The main aims of this study were the evaluation of the frequency and clinical characteristics of NC following H1N1 flu vaccine administration in Switzerland.

Frequency

The vaccination coverage was approximately 17% and thus comparable to other central European countries. On the basis of the calculated number of 40 newly diagnosed cases of narcolepsy per year (including post-H1N1 NC), the notified total number of (8) 9 post-H1N1 vaccination cases is within the normal range and primarily does not indicate an elevated risk. An increase of narcolepsy diagnoses was mainly found in children and adolescents [17, 18], in Scandinavian countries in particular [19]. In Switzerland, Pandemrix® has not been applied in children and adolescents. This likely had an impact on the (probably) normal number of narcolepsy cases occurring. Additional epidemiological data, incidence data most notably, are needed for Switzerland.

Clinical Characteristics

Some recent studies have reported on specific features in post-H1N1 vaccination narcolepsy. Dauvilliers et al. [9] described an abrupt and severe onset of EDS and cataplexy and Pizza et al. [20] found higher numbers of post H1N1 NC patients with disturbed sleep. Our results are in line with these findings. In addition, we found high numbers of sleep paralysis and hallucinations immediately being present at disease onset. Our data support the description of post-H1N1 vaccination NC showing a 'full-blown' spectrum from the onset of disease.

Clinical Course – Evolution

There are limited data on the spontaneous course of post-H1N1 vaccination narcolepsy. Almost all of our patients (7/8) received symptomatic pharmacological treatment. Hence, improvement of EDS, as described by a majority of the patients can be explained by the treatment. Only 3 patients were treated with specific drugs against cataplexy, but almost all patients described an improvement of this symptom in the early course. In a majority of patients, sleep fragmentation, sleep-related hallucinations and sleep paralysis also became less, later on.

A remarkable, spontaneous improvement of cataplexy has been described in sporadic NC [21], and is therefore not an exclusive feature of post H1N1 NC.

Limitations of this study include the retrospective study design, small sample size and lack of epidemiological data.

The temporal association of H1N1 flu vaccination and narcolepsy and suggested specific clinical features in post-H1N1 vaccination narcolepsy strengthen the hypothesis of an autoimmune process as a driving force in the pathogenesis of narcolepsy.

Long-term studies from countries with higher H1N1 vaccination rates are needed to better evaluate the clinical characteristics and course of post H1N1 NC.

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Disclosure Statement

All authors declare no conflict of interest. RH is member of the Nightbalance advisory board.

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